

**“Requiring adolescent informed assent
in clinical research trials”**

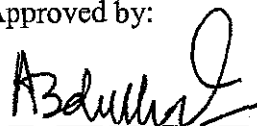
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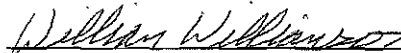
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Introduction

For many years, the process of voluntary informed consent for adult clinical research subjects has been widely accepted, standardized, and federally regulated. In comparison, adolescent clinical research subjects were not afforded the same privileges. Within the past decade there has been an increase in the number of pediatric and adolescent clinical research trials in the United States (NCCF 2000). Consequently, the moral and ethical implications of clinical research on minors has become a widely discussed issue and the notion of adolescent assent – a minor’s affirmative agreement to participate in a clinical research trial – has been recognized. The purpose of this paper is to discuss the current and future use of adolescent assent in clinical research trials.

What is informed consent?

To best understand the need for adolescent assent, it is necessary to first understand the adult informed consent process and discuss its history, required elements, and relevance. The process of informed consent arose from the idea of bodily autonomy. Specifically, the notion of informed consent comes from the Nuremberg Code, which was adopted after the horrific discovery of research conducted by the Nazi party on prisoners of war. The Nuremberg Code begins by stating, “the voluntary consent of the human subject is absolutely essential.” The Code goes on to address many of the issues that are now required elements of an informed consent. The Code can be viewed as Appendix A.

In 1964, the World Health Organization recognized the need to better provide guidelines that govern biomedical research and clinical trials. At their conference, the Declaration of Helsinki was unveiled which detailed ethical principles for medical research involving human

subjects. The Declaration serves as a “subject bill of rights” and gives subjects the right to ongoing information during the trial. The Declaration is attached as Appendix B.

Today’s informed consent is the ongoing process by which an investigator and study staff explains, answer questions, assess participant understanding, and document a subject’s agreement to participate in a clinical trial. Informed consent is always obtained prior to the start of any study related procedures and must be documented in the subject’s medical chart. Per the Code of Federal Regulations (2002), the informed consent process must include a discussion of certain elements that outline the trial and help the subject better understand the risks, benefits, alternative procedures, and purpose of the study. The discussion can include family members and, in fact, some institutions encourage subjects to bring the consent home for review prior to signature.

The informed consent process is ongoing throughout a subject’s participation in the study. Subjects are always informed of new information and informed consent forms are altered to reflect significant changes to the study design or protocol. As provided by the Nuremberg Code, informed consent to participate in a research trial is voluntary and may be withdrawn at any time. Informed consents for adult patients should be generated at an 8th grade reading level and should be in the subject’s natural language. There are 14 required elements of informed consent as directed by 21CFR Subpart B 50.25. These are listed in Appendix C.

Adolescents in research

The increase of adolescent participation in clinical research stems from the 1994 Food and Drug Administration (FDA) final rule designed to ensure that new drugs and biological products contain adequate pediatric labeling for the approved indications. The final rule

establishes that all new drugs and biologics will be studied in pediatric patients, and states that pediatric patients should not be excluded from pharmaceutical studies based solely upon inclusion into this population. The rule also authorizes the FDA to require pediatric studies of those marketed drugs and biological products that: (1) are used in a substantial number of pediatric patients for the claimed indications, and where the absence of adequate labeling could pose significant risks; or (2) would provide a meaningful therapeutic benefit over existing treatments for pediatric patients, and the absence of adequate labeling could pose significant risks to pediatric patients (21 CFR Parts 201, 312, 314 and 601). Additionally, the FDA argues that many diseases only affect children and it is, therefore, only appropriate that children participate in these trials to assure proper dosing and administration of medicine as well as growth and psychosocial side effects.

While the concept of adolescents in research is new, studying adolescents in the medical setting is not. Clearly documented are problems regarding follow up, noncompliance, continuity of care, trusting relationships, and confidentiality (Wilson 2000). Pharmaceutical companies and physicians rely heavily on patient reported symptoms, medication usage, and side effects. Including adolescents in research studies must be carefully weighed by the physician, in cooperation with parents, to determine if the adolescent is capable or likely to adhere to a study regimen.

Federal regulations

In contrast with current physician ideology and Health and Human Services (HHS) policy, current federal regulations require only parental consent for all clinical drug trials. The FDA does recommend obtaining adolescent assent if possible but does not specify the age from

which assent is required nor the form the assent process should take. Specifically, 21 CFR Subpart D 50.55 states that “In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.” The Code continues by stating that the principal investigator and the Institutional Review Board (IRB) are left to determine the psychological state and maturity of the child, the type of assent issued and, ultimately, the need for assent.

According to the Code, assent is defined as “a child’s affirmative agreement to participate in research,” and should be sought in addition to parental informed consent or permission if the minor adolescent is sufficiently able to understand the nature of participation in the clinical trial (45 CFR Part 46). The crafting of an assent process should be viewed as a collaborative effort between investigator and the IRB. Due to the vague doctrine in the Code, regulation by IRBs is not standardized. IRBs are panels of medical specialists, nurses, social workers, and patient advocates who review clinical trial protocols, informed consents, patient information, and proceedings at institutions that conduct medical research. Each IRB has its own requirements for how trials can be conducted and what information must be provided to participants. Therefore, assent requirements vary greatly from institution to institution.

Although there is no federal mandate or standardization, several pediatric groups have issued recommendations regarding adolescent assent. The Department of Health and Human Services published an Institutional Review Board Guidebook that states “the child should be given an explanation of the proposed research procedures in a language that is appropriate to the child’s age, experience, maturity, and condition. This explanation should include a discussion of any discomforts and inconveniences the child may experience if he or she participates.” The

Federal Register (2000) also points out that distress is to be minimized for minors in clinical trials. Practices to consider to ensure minimal distress include staffing the trial with knowledgeable and skilled personnel with a specialty in pediatrics, having a physical setting conducive to the population (X-box games in lieu of Newsweek magazine), conducting the study in a familiar environment such as a routine clinic, and minimizing the number of blood draw attempts, sticks, and the amount of blood drawn. The Children's Health Act of 2000 requires that all research involving children be in compliance with HHS regulations, and that there be a waiver of the FDA rule that disallows waivers for parental permission.

Current overall exceptions to the parental permission rule in medicine vary state to state, but in most cases adolescent minors can give consent for pelvic examinations, screening for and treatment of sexually transmitted diseases, counseling for and prescribing of contraception, sexual abuse and mental health treatment, and HIV testing. Twenty-two states require adolescent minors to notify parents prior to an abortion and nineteen states require parental consent prior to abortion. Nine states have no laws regarding the matter. Most states, however, require parental notification and some states require parental signature (Kendell 2000).

The social obligation of adolescent assent

It is now widely recognized that the doctrine of "informed consent" has only limited direct application to adolescent minors, as only patients can directly give informed consent for their care (American Association of Pediatrics 1995). In situations that require a parent or surrogate to make the decision, *informed permission* is provided by the parent and *informed assent* is provided by the minor adolescent patient.

As provided by the Nuremberg Code and Declaration of Helsinki, participation in clinical trials must be voluntary and the subject must remain informed throughout the study. Although the assent process is largely left up to the discretion of the investigator, the American Academy of Pediatrics (1995) agrees that IRBs and the investigator must consider how a subject's maturity will be assessed, who will obtain assent, where and when parental permission and child assent will be obtained, what types of assent documents will be used, whether signed assent will be requested, how the child's assent will be documented by the researcher, how it will be determined whether subjects/parents understand the research, and justification of a waiver of parental permission or child assent, if necessary. The Children's Hospital of San Diego and the Children's Hospital IRB were among the first to create an adolescent assent form (CCI/IRB 1993). This form is widely used as a template (Appendix D).

Providing adolescent assent assures elements of understanding regarding the clinical trial and fosters cooperation. The rights and dignity of the adolescent should be respected by empowering the adolescent with the knowledge needed to take part in his or her medical treatment (SIOP 2003). As adolescents become more autonomous in healthcare decisions and more knowledgeable about the field of medicine through television and the internet, physicians have been forced to abandon traditional paternalistic practices and better inform their patients of treatment options. In fact, healthcare is now seen as a partnership, where both the physician and patient make joint decisions and each has the right to agree or disagree to an action plan. Other societal disciplines, such as law, have already held adolescents to a higher moral and cognitive standard as is evidenced by the disturbing trend in criminal law to lower the age of responsibility for violent crimes and prosecuting these adolescents as adults (Aiken 2001). It is this concept of adolescent autonomy and self-responsibility that drives the notion of informed assent.

Other benefits to adolescent assent

Adolescent assent encourages active participation in the medical decision process. Specifically, providing assent encourages understanding of the subject's illness, potential treatments, and the clinical trial while empowering the adolescent to ask questions and make determinations regarding his or her care. Giving the adolescent ownership of medical decisions will also foster compliance, a known issue with adolescents (Ziv 1999). Additionally, adolescents who have an active participation in the assent process are more likely to utilize physician offices for primary care rather than the emergency room (Wilson 2000). Adolescent assent also aides in breaking down other barriers to healthcare for adolescents, which include access to care, costs, confidentiality, privacy, confusing state and federal laws, and the ability to consent to care. Of these, disclosure of confidential information to parents and lack of understanding of state and federal laws are the biggest perceived obstacles by adolescents (Klein, 1999 and 1998).

Adolescent assent also has industry implications, in that it provides pharmaceutical companies and physicians with an insurance against future lawsuits of children injured while participating in clinical trials. Additionally, these companies and physicians expressed concern at the 1994 FDA hearings that ethical concerns of children were often overlooked in clinical practice and better standards should be set forth to ensure protection of rights. Pharmaceutical companies, more often than not, will provide an adolescent assent template for any clinical trial that enrolls this population (CCI/IRB 1993).

The adolescent assent process

As is the case with adult informed consent, the informed assent process implies more than just reading and signing a form. The informed assent process must include a discussion of the clinical research trial between the adolescent minor and the principal investigator. In most cases, explanation of consent and discussions last approximately 10 minutes per informed consent page (CCI 1993). After a thorough explanation of the procedures of the trial, the investigator must answer all questions of both the parent and the minor, ask questions to determine if the parent and the adolescent fully understand their risks, benefits, and treatment options, and make a final determination as to whether or not the participant understands the pertinent information of the trial. Additionally, with adolescent subjects, an investigator and the IRB must determine (1) if the subject is a minor adolescent, (2) the subject's cognitive ability, (3) the level of confidentiality to be maintained and (4) how to obtain assent.

The adolescent assent process – defining a minor adolescent

According to state and federal law, persons under the age of 18 years are considered minors. In general, these patients cannot give informed consent about healthcare decisions for themselves. Instead, healthcare decisions are made by a parent or legal guardian. In an emergency, when a parent or legal guardian is unable to give consent, a physician assumes the responsibility of consent and uses his or her discretion regarding treatment of the minor. Those exempt from minor adolescent status include emancipated and mature minors. Emancipated minors are defined as adolescents who are married, pregnant, a parent, military, or self-supporting. Mature minors are those deemed to have sufficient cognitive and psychological

maturity to make medical decisions as if they were 18 years or older. To become a mature minor, an adolescent must attend a judicial proceeding where a judge grants such status.

The adolescent assent process – determining cognitive ability in minor adolescents

Adolescent assent implies that the subject giving assent understand the benefits and risks of treatment – or of refusing treatment. As stated by the Code of Federal Regulations, IRBs and investigators are to determine the adolescent’s capability of providing assent. While cognitive development is one of the most expected aspects of a minor’s growth and educational experience, development varies greatly between students of all socio-economic backgrounds making determination of true cognition a difficult task (ADOL 1997).

A study by Tait et al (1998) showed that children’s perceived level of understanding of the elements of disclosure was significantly greater than their measured understanding. In fact, complete understanding of the elements of informed consent ranged from 30.4 to 89.4%. Children over the age of 11 had a significantly greater understanding with respect to the study protocol, potential benefits, and voluntary participation.

Based upon similar studies, the National Commission for Protection of Human Subject of Biomedical and Behavioral Research (2001) established age 7 as the minimum age for involving children in the assent process. It is felt that most children this age can understand information tailored for their developmental level. Still, assessing children’s maturity based solely on chronological age may not provide an accurate picture of their capacity to understand the research or to give assent. Therefore, the American Academy of Pediatrics recommends that assent “should usually be obtained from any child with an intellectual age [rather than chronological age] of 7 years or more.”

For adolescents, a normal teenager's development can be divided into three stages – early, middle, and late adolescence (ADOL 2003). Early adolescence includes minors aged 12-14 years. Generally, in this age group, adolescents are moving towards independence and struggle with a sense of identity. There is often moodiness, outbursts of feelings, and a distancing from parents. The early adolescent has improved speech abilities and is better able to articulate his or her ideas but is unable to have a sense of self direction and little regard for ethics or health status. Middle adolescence (15-16 years of age) is characterized by self improvement, vanity, and examination of priorities. These adolescents are most concerned with sexual attractiveness and feelings of intimacy. Ethically, middle adolescents begin their development of ideals and select role models. Middle adolescents will have a high interest in health as it relates to looking and feeling better. Late Adolescence, those aged 17-19 years, shows firmer identity, greater emotional stability, and self reliance. This group is able to delay gratification, is more concerned with the plight of others, and is capable of useful insight. These adolescents are often proactive about their moral and ethical obligations to society and their participation in preventive healthcare.

The adolescent assent process – maintaining confidentiality

According to the American Academy of Pediatrics' Dr. Jenkins (2002), "Research has shown that a majority of adolescents voluntarily share information with their parents after they consult privately with their health provider." Additionally, adolescents are more likely to seek routine healthcare if they can be assured that their confidentiality will be maintained (Thrall, 2000). Together, physicians, parents, and adolescents should determine the type of disclosure (full, partial, none) that will occur between the physician and parent regarding the adolescent.

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) includes privacy regulations for adolescents. The act is intended to assure patients that private health information will be kept confidential and only limited information will be disclosed for purposes other than patient care (HIPAA 1996). The rules currently allow parents access to the private health information of minor adolescents but can be overridden by more protective state and local laws. Due to the vagueness of the Act and lack of support from the current Bush administration, most physicians obey local laws but use their own discretion regarding whether or not to provide parents with information about basic care (American Medical Association 1998).

In contrast to HIPAA regulations, the FDA requires parental permission and access to confidential records with regard to clinical trials. In a 2001 letter to the FDA, the National Human Research Protections Advisory Committee, a Division of the US Department of Health and Human Services (US DHHS), asked that “the FDA utilize an aggressive interpretation of the Food Drug and Cosmetic Act to enable mature adolescents to consent to involvement in certain types of important clinical studies without parental permission.” The FDA replied that it was aware of the parental permission and confidentiality discrepancies between HHS, HIPAA, and the FDA but has made no means to decrease the disparities.

The adolescent assent process – obtaining adolescent assent

The National Childhood Cancer Foundation (2002) recommends that adolescent assent be obtained at the same time as parental consent. The Foundation maintains that consents are best presented to families in a simple and straight-forward manner. Discretion should be used when choosing the timing and location of when and where consent will be obtained so that the child and parents will be given an undistracted, ample amount of time to fully understand the purpose,

risks, benefits, alternate options, compensations, and other factors that may influence participation. The Foundation strongly believes that the decision should be family centered and not rushed or coerced by staff and that the subjects should not be overburdened with all of the information prior to a critical procedure. It is widely considered unfair to give an adolescent and family a diagnosis, begin discussing a trial, and push for consent on the same day. Rather, the entire family should be encouraged to ask questions and the researcher should not only answer questions but should also ask questions to assure understanding.

The International Society of Pediatric Oncology (SIOP 2003) adds two more recommendations. In addition to the above, it states that children have a right to be treated with the best medical intervention available (regardless of parental permission issues) and that parents do not have the exclusive right to be the sole decision maker. The Society pushes for court intervention when necessary for older adolescents and believes strongly that children of all ages should be included.

If the subject's intellectual capabilities fall within the range of a 7-12 year old, a child information form should be required in addition to the parental permission form. The form should be brief and specific, containing an explanation of the procedures, risks, and benefits. The form must be written in a language that is appropriate to the child's maturity and should not exceed 2 pages. Pictures and larger text should be used when possible (KIDLINK).

For adolescents over the cognitive age of 12 years, an adolescent assent form should be used that mirrors the adult informed consent form (Appendix D). The assent process should include a candid discussion with the investigator about the risks, benefits, procedures, and treatment in the clinical research trial, the use of the assent form, a question and answer session, and a determination by the physician of the subject's understanding.

Elements in adolescent assent

Although federal regulations do not dictate required elements of assent, the American Academy of Pediatrics (1995) has set forth its own criteria to aid IRBs and investigators. These are: (1) helping the patient achieve a developmentally appropriate awareness of the nature of his or her condition; (2) telling the patient what he or she can expect with tests and treatment (s); (3) making a clinical assessment of the patient's understanding of the situation and the factors influencing how he or she is responding (including whether there is inappropriate pressure to accept testing or therapy); (4) soliciting an expression of the patient's willingness to accept the proposed care. Regarding this final point, the Academy notes that no one should solicit a patient's views without intending to weigh them seriously. The adolescent minor should be told upfront that dissent may still result in participation in the clinical trial. An adolescent's failure to object to assent should not be misconstrued as assent and the investigator should determine prior to the start of study procedures if the subject is truly assenting to the study.

Adolescent dissent and parent permission

The minor has the right to dissent at any time. Dissent, however, can be dismissed if either the minor is determined to be mentally or physically unable to provide assent or the research intervention is the only available treatment option. In this case, the parent permission or consent overrides the adolescent assent. Investigators conducting research must be sensitive to a subject who dissents and try to foster compliance and trust with that subject. Should the dissenting adolescent become uncooperative, difficult decisions must be made by the physician on how to proceed to assure that the adolescent remains informed and treated appropriately (Lim

2003). The American Medical Association's Policy H-60.965 states that parental consent should not be a barrier to adolescent care and that adolescent consent should be obtained whenever possible.

In cases of minor adolescent dissent with parental permission, an information sheet should be provided to the minor adolescent. The information sheet should contain the same information as the assent form but with the signature removed. The investigator should acknowledge in the subject's medical chart that parental permission was obtained, adolescent minor permission was denied, and due diligence to inform the subject of participation was provided in the form of an information sheet (Lim 2003).

The case against assent

It has been argued that it is nearly impossible for an investigator to determine a minor's psychological capacity to know if assent should be provided, especially if the investigator is not the subject's primary care provider (Aiken 2001). It is equally hard to discern if adolescents are capable of making decisions that will affect them for the rest of their lives at an age when they are prone to vanity and social pressures. Noncompliance is a continual problem in adolescents, especially when the treatment regimen includes altering normal features (such as steroid use) (Thrall 2000). To diffuse these arguments, an empirical study should be undertaken to determine the cognitive age at which adolescents comprehend the informed consent process for clinical trials.

Conclusion

Once adolescent minors become capable of making autonomous decisions about their own beings, it is morally and ethically imperative that their decisions be solicited and respected. It is the responsibility of the FDA, HHS, American Academy of Pediatrics, and other interested parties to provide standardized guidance regarding the rights and protection of adolescent subjects just as is done for adults. Once there is clear direction and convergence from these governing bodies, a mandate for adolescent informed assent must be written into the Code of Federal Regulations to empower the adolescent research participants of the future.

Inherent in clinical trial research is the affirmation that participation is voluntary and that the subject is made aware of the risks, benefits, and treatment options. With a current trend, via HIPAA and HHS, toward adolescent confidentiality, the need for assent is even greater to ensure that the minor adolescent is given every opportunity to be properly informed and permission granted for research. Informed assent is the vehicle that drives this autonomy for adolescent research participants. While the FDA, HHS, American Academy of Pediatrics, investigators, and IRBs agree that adolescent assent should be obtained whenever possible, there is little standardization across institutions regarding when, where, and how to obtain consent.

It is agreed, however, that the assent process should include a determination if the subject is a minor adolescent, of the subject's cognitive ability, of the level of confidentiality to be maintained and how to obtain assent. Children with a cognitive age of 7 or greater should be included in the assent process. The assent process must include a thoughtful discussion between the minor subject and the investigator regarding participation in research. For minor adolescents with a cognitive age 13-17 years of age, an adolescent assent form should be required that follows the format provided for adult consent but contains appropriate language relative to the

educational level of the youngest possible participant. The adolescent assent form must contain all 14 required elements of the informed consent as outlined in Appendix C. Specific focus should be placed on helping the patient fully understand the nature of his or her health condition, an explanation of what he or she can expect with tests and treatment, making a clinical assessment of the patient's understanding of the situation and the factors influencing how he or she is responding and a testament from the patient regarding the willingness to accept the proposed care. As is the case with adult informed consent, all assent processes must be fully documented in the subject's medical chart. Adolescent dissent must also be documented and appropriate steps taken to ensure that the adolescent's treatment is not compromised.

Appendix A

NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Appendix B

Declaration of Helsinki

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient. " The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease. In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects. In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research. Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the

World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the law of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

Appendix B (continued)

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who isn't engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present declaration are complied with.

Appendix B (continued)

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient- including those of a control group, if any- should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers- either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Appendix C

Elements of Informed Consent

1. A statement that the study involved research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others that may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that FDA may inspect the records.
6. For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of who to contact for answers to pertinent questions about the research and the rights of the research subjects, and who to contact in the event of a research-related injury to the subject.
8. A statement that participation is voluntary, that refusal to participate involves no penalty or loss of benefits to which the subject is otherwise entitled.

The following additional elements, when appropriate, are also required:

9. A statement that the particular treatment or procedure may involve risks to the subject (or the embryo or fetus, if the subject is pregnant or may become pregnant) that are currently foreseeable.
10. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
11. Any costs to the subject that may result from participation in the research.
12. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
13. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject.
14. The approximate number of subjects involved in the study.

Appendix D

Adolescent Assent Form (ages 13-17)

Title of Protocol

This is a research study. Research studies include only subjects who choose to take part. You are being asked to take part in this study because you have Please take your time to make your decision. Talk to your family about it. Be sure to ask questions about anything you don't understand.

STUDY INVESTIGATOR AND SPONSOR

Investigator:

Sponsor:

WHY IS THIS STUDY BEING DONE?

This study is being done to find out.....

WHAT MAKES THIS DIFFERENT FROM THE USUAL TREATMENT?

The experimental part of this study is(example: using the new drug called _____. This is an experimental drug because the Food and Drug Administration has not approved this drug to be used outside of a research studies like this one.)

Another experimental part of this study is(example: that you will be randomized into one of three study groups. Randomization is like tossing a coin to make a choice. Neither you or the study doctor will choose your study group; it will be a random choice.)

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

___ subjects will be in this study.

HOW LONG WILL MY CHILD BE IN THE STUDY?

You will be in the study for _____.

You can stop being in the study at any time. But, if you decide to stop, we encourage you to talk to the research doctor first.

Appendix D Continued

WHAT IS INVOLVED IN THE STUDY?

This is what will happen if you are in this study:

Study Visit 1: These tests will be done at this visit.

Study Visit 2: These tests will be done at this visit.

We will let you know if there are any changes to the study or any new information that may change your mind about being in this study.

WHAT ARE THE RISKS OF THE STUDY?

The most common side effects seen with _____ are:

Side effects seen less often are:

If you get sick or have any problems from taking the study drug you should call your study doctor right away. If necessary, using the study drug may be stopped and other therapy may be started.

Blood Draws: Possible side effects from blood drawing include:

faintness,

irritation of the vein,

pain,

bruising

or bleeding at the blood draw site.

There is also a slight possibility of infection or fainting.

Using the numbing cream used for blood draws may cause pain, skin irritation, or the skin temporarily turning red, white or developing a rash.

Other risks in this study include the following:

Your condition may not improve, it may stay the same or it may get worse while you are in this study. There may be side effects or discomforts from the use of the study drug, that we don't know about yet.

For more information about risks and side effects, ask your study doctor.

Appendix D (continued)

For Girls: Are There Risks if I Get Pregnant?

There may be unknown risks to an unborn baby if you are pregnant and participate in this study. *Sample wording: So, if you are having menstrual periods, you must use a study approved birth control method and agree not to try to get pregnant during the study.*

It is important that you contact the study doctor right away if you think you may be pregnant, if you have missed a period or it is late, or if you have a change in your usual menstrual cycle (heavier bleeding than usual or bleeding between periods).

If you become pregnant during the study you will not be allowed to stay in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Sample wording: We cannot promise that you will benefit from this research study. You may get better or you may get worse. Others may benefit from the information gathered from this study.

WHAT OTHER OPTIONS ARE THERE?

Sample wording: If you choose not to be in this study there are other options available that you can talk about with the doctor. Some other options are:

WHAT ABOUT CONFIDENTIALITY?

Every reasonable effort will be made to keep your medical records confidential. But we do have to let some people look at your study records and maybe your hospital records. These people can see your records:

(sponsor)
The FDA (US Food and Drug Administration) or governmental agencies in other countries where the study drug may be considered for approval
The IRB (for the protection of human subjects in research)

We will keep your records private unless we are required by law to share any information. The law says we have to tell someone if you might hurt yourself or someone else. The study doctor can use the study results as long as you cannot be identified.

WHAT ARE THE COSTS?

WHAT IF I AM INJURED IN THE STUDY?

If you need to be treated for any research injury or illness from being in this study you will be given medical care.

Appendix D (Continued)

WILL I GET PAID TO BE IN THIS STUDY?

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, call the researcher:

Name and phone number

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Being in this study is voluntary. You don't have to be in this study if you don't want to or you can stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits that you have now. If you have questions about your rights you may call:

Rebecca M. Clark, IRB Coordinator (858) 966-4008
Institutional Review Board
(which is a group of people who review the research to protect your
rights)

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Appendix D (Continued)

AGREEMENT TO BE IN THE STUDY

Your signature below means that you have read the above information about the _____ study and have had a chance to ask questions to help you understand what you will do in this study. Your signature also means that you have been told that you can change your mind later if you want to. You will be given a copy of this agreement and a copy of the Subject's Bill of Rights. By signing this assent form you are not giving up any of your legal rights.

SIGNATURE OF SUBJECT (13 YRS & OLDER)

DATE

SIGNATURE OF PERSON WHO EXPLAINED THIS FORM

DATE

Appendix D (Continued)

ADOLESCENT SUBJECT BILL OF RIGHTS

As a subject in a research, you have certain rights and responsibilities. It is important that you understand the nature and purpose of the research and that your consent be offered willingly. To help you understand, you have the following specific rights:

1. To be told about the research and why it is being done.
2. To be told about all procedures to be followed and of any drug or device to be used.
3. To be told about any risks or discomforts, which can be reasonably expected to happen.
4. To be told about any benefits you may expect as a subject of this research.
5. To be told about any other options you have instead of this research.
6. To be told about any medical treatments that are available to you if there are complications from this research.
7. To be encouraged to ask questions and given a chance to ask any questions about the study or the procedures involved in this research.
8. To be told that you can stop being in this research study at any time and that won't affect your medical care in any way.
9. To be given a copy of the signed and dated written assent form.
10. To not be pressured in any way to be in this research study or be pressured to choose not to be in this research study.

If you have any more questions or are worried about your rights as a research subject, please call your research doctor or Rebecca Clark, IRB (human subjects) Coordinator at 858-966-4008 during normal working hours.

SUBJECT SIGNATURE

DATE

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